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SOLUBILITY PARAMETERS FROM MAXIMA IN SOLUBILITY/SOLVENT PLOTS

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SUMMARY

Solubility data of a substance in solvents with known solubility parameters have been used graphically in the past to determine the solubility parameter of the solute. A multiple regression method of handling this is presented. It gives rise to self-consistent solubility parameters, but the solvent molar volumes calculated are anomalous, pointing to the presence of factors not accounted for in the traditional approach to solubility parameter determination through solubility determination.

INTRODUCTION

There has, through the last 3 decades, been a consistent pharmaceutical interest in solubility problems, witnessed by several pioneering articles (Hildebrand et al., 1970, Amidon et al., 1974, Restaino and Martin, 1964, Schwartz and Paruta, 1976, Hildebrand and Scott, 1962, Chertkoff and Martin, 1960 and Alexander et al., 1977). Most of the theoretical approaches to solubility take their basis in the work by Hildebrand and Scott (1962) in particular by using, as a starting consideration, the regular solubility of a compound. This is obtained by the expression (Hildebrand et al., 1970):

$$\ln X_2 = -(\Delta H/R) \cdot \{(1/T) - (1/T_m)\} - (\delta_1 - \delta_2)^2 \phi_1{}^2 (V_2/RT) \tag{1}$$

where X_2 is here the solubility of the solute (subscript '2') in the solvent (subscript '1'), ΔH is the heat of fusion of the solute at the melting point, T_m, T is the temperature of the study, δ is the solubility parameter, ϕ is the volume fraction in solution at solubility and V is molar volume.

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TABLE 1

LEAST SQUARES PARAMETER AND DERIVED VALUES FOR PARAHYDROXYBENZOIC ACID ESTERS

	Methyl [a]	Ethyl [a]	Propyl [a]	Butyl [b]	Butyl [a]	Benzoic acid[a]
Molar volume (V_2) (ref. 3)	121	140	158	106	176	101
ΔH (cal/mol)	4352	4243	4026	3737	3737	4302
T_m	400	390	370	343	343	395
a	−36.7	−28.2	−14.3	−8.51	−9.63	−109.4
b	6.58	5.09	2.64	1.61	1.94	19.54
c	−0.295	−0.230	−0.126	−0.078	−0.102	−0.869
R^2 [a]	0.826	0.891	0.992	0.937	0.980	0.924
δ_2 from Eqn. 3	11.2	11.1	10.8	10.37	9.93	11.2
δ_2 (ref. 3)	11.0	11.3	10.9	11.0	11.0	11.2
V_2 (Eqn. 5/6)	174	136	72.3	46.0	58.0	51.4
V_2 (Eqn. 7)	175	136	74.8	46.2	60.5	516

[a] Values based on ideal ϕ_1-values.

[b] Values based on experimental ϕ_1-values.

By testing the solubility of a solute in various solvents of different solubility parameters, the solubility parameter of the solute is often found by locating the maximum in the X_2 vs δ_1 curve (Restaino and Martin, 1964). It may be seen (Table 1) that this leads to quite acceptable values of the solubility parameter of the solute (and this indeed was the purpose of the reported experiments). In cases where X_2 vs δ_1 does not present a curve with a sharp maximum, such a graphical method may have its shortcomings. However, conventional multiple regression procedures will overcome this as described in the following. Eqn. 1 is recast in the following form:

$$z = a + b\delta_1 + c\delta_1^2 \qquad (2)$$

where

$$z = (1/\phi_1^2)(\ln X_2 + (\Delta H/R)\{(1/T) - (1/T_m)\}) \qquad (3)$$

$$a = -(V_2/RT)\delta_2^2 \qquad (4)$$

$$b = 2(V_2/RT)\delta_2 \qquad (5)$$

and

$$c = -V_2/RT \qquad (6)$$

If X_2 is known for a substance dissolved in a series of solvents with different δ-values, and if ΔH and T_m are known for the substance (solute), then z can be calculated for each solvent, and the parameters a, b and c obtained via Eqn. 2 by multiple regression. It is noted that

$$\delta_2 = -2a/b \tag{7}$$

Once this is calculated, V_2 can be calculated from either Eqns. 4 or 5, and should correspond to the V_2-value obtained from Eqn. 6.

MATERIALS AND METHODS

The solubilities of methyl-, ethyl-, propyl- and butyl-parahydroxybenzoates in *n*-propanol, *n*-butanol, *n*-pentanol, *n*-hexanol and *n*-octanol (all with known solubility parameters) have been reported by Restaino and Martin (1964) and these values have been used to test Eqns. 2–6.

Reported ΔH-values and T_m-values from the same source have been used to calculate z. The influence of actual vs ideal densities was tested in the study, and for this reason the partial molar volumes of both solvent and solute at the solubility concentration need to be known. This was achieved by determining densities of solute in solvent pycnometrically by use of a 25.00 cm^3 pycnometer and a waterbath with temperature accuracy of 0.1°C, and performing this at a large number of concentrations.

RESULTS AND DISCUSSION

For binary mixtures where both δ_1 and δ_2 are known, it is possible to deduce the values of ϕ_1 and ϕ_2 by the following iteration procedure (Hildebrand and Scott, 1962): unity is taken as the first estimate of ϕ_1, and a mole fraction, x_2, is calculated from the equation:

$$\phi_1 = \frac{(1 - x_2) V_1}{(1 - x_2) V_1 + x_2 V_2} \tag{8}$$

The value of x_2 is inserted in Eqn. 9 below:

$$\ln X_2 = -(\Delta H/R) \cdot \{(1/T) - (1/T_m)\} + \{\Delta C_p/R\}\{(T_m - T)/T\} - (\Delta C_p/R) \cdot \ln (T_m/T) - (V_2/RT)(\{\delta_1 - \delta_2\}^2 \phi_1^2) \tag{9}$$

ΔC_p in this equation denotes the difference in molal heat capacities of liquid and solid. By iteration, values of ϕ_1 are found, which have internal consistence. If δ_2 is not known, then this method does not apply. In the following the approach is used to obtain ϕ_1 from density data.

As mentioned under Materials and Methods densities (ρ) were determined at various compositions, and the total molar volume V of the mixture obtained as

$$V = M/\rho \tag{10}$$

where M is the composite molecular weight given by:

$$M = X_1 M_1 + X_2 M_2 \tag{11}$$

TABLE 2

DENSITIES OF SOLUTIONS OF BUTYL-PARAHYDROXYBENZOATE IN *n*-PROPANOL

x_2	$(x_2)^2$	Mol. wt., M (eqn. 11)	Mol vol. $V = M/\rho$ (cm^3)	V [a] (cm^3)	V (ideal) (cm^3)
0.0375	0.00141	65.03	80.12	80.18	79.97
0.0728	0.00530	67.76	83.68	83.71	83.49
0.1094	0.01197	74.66	87.51	87.39	87.14
0.1371	0.01880	78.37	90.35	90.20	90.17
0.1658	0.02749	82.22	93.14	93.12	92.77
0.1903	0.03621	85.50	95.30	95.63	95.22
0.2380	0.05664	91.89	100.62	100.54	99.98
0.2830	0.08009	97.92	105.32	105.21	104.46
0.3113	0.09691	101.71	108.10	108.17	107.29
0.3601	0.12967	108.25	113.32	113.31	112.16

[a] The least-squares fit equation according to Eqn. 12 is:

$V = 76.45 + 99.007\ x_2 + 9.2823\ x_2^2$ (correlation coefficient = R^2 = 0.9998). V is then the value calculated for the corresponding x_2-value.

Data from the least ideal case (butyl-parahydroxybenzoate in *n*-propanol) are shown in Table 2.

The relation between V and X_2 is approximated as a polynomial (Maron and Prutton, 1965):

$$V = \alpha + \beta x_2 + \gamma x_2{}^2 \tag{12}$$

where the polynomial constants, α, β and γ are obtained by least-squares fit multiple regression. The constants for the various solvent pairs, and the correlation coefficients are shown in Table 3. Specific comparisons between predicted and obtained values and further comparisons of this with the ideal value are shown in the case of butyl-parahydroxybenzoate in *n*-propanol in Table 2. It is noted that Eqn. 12 describes the relations well (correlation coefficients being close to unity).

TABLE 3

VALUES OF THE PARAMETERS α, β AND γ (EQN. 12) FOR BUTYL-PARAHYDROXYBENZOATE IN VARIOUS SOLVENTS

Solvent	α	β	γ	Correlation coefficient, R^2
n-Propanol	76.451	99.007	9.282	0.9998
n-Butanol	91.575	104.383	−43.460	0.999
n-Pentanol	110.312	64.321	11.684	0.9999
n-Hexanol	127.018	50.579	4.791	0.9997
n-Octanol	161.706	8.192	24.978	0.979

The partial molal volume ($\bar{V}_1$) of the solvent at solubility (X_2) is found using the equation (Maron and Prutton, 1965):

$$\bar{V}_1 = (\alpha - \gamma X_2^2)/x_1 \tag{13}$$

It is now possible to calculate ϕ_1. In the case of butyl-parahydroxybenzoate (mol. wt. 194) dissolved in propanol (mol. wt 60), ϕ_1, when calculated by assumption of ideality has a value of 0.430. This is obtained by noting that the molar volume of butyl-parahydroxybenzoate is 176 cm^3/mol, so that 0.6466 g (the solubility in 1 g of solution) occupies 0.5866 cm^3. Since 1 g of solution occupies 1.0284 cm^3, it follows that the solvent occupies 0.4418 cm^3, giving $\phi_1 = 0.4418/1.0284 = 0.430$. However, when experimental data are used in Eqn. 13 (noting $X_2 = 0.361$) $V_1 = 117.8$ cm^3. Using values of β and γ from Table 3 it is found that $\bar{V}_2 = \beta + 2\gamma X_2 = 105.7$ cm^3. From the value of $\bar{V}_1$ and $\bar{V}_2$ the value of $\phi_1 = 0.664$ is obtained via Eqn. 8. This differs considerably from the ideal value quoted above. It is noted, however, that this is the least ideal of the cases quoted here. Calculations of z can now be made with either ideal or experimental values of ϕ_1. For the ideal case, for instance, $\Delta H = 3737$ cal/mol, $T_m = 343.15°K$ and $\ln X_2 = -1.019$, for butyl-parahydroxybenzoate in *n*-propanol. Hence:

$$z = (1/0.1845) \cdot (-1.019 + (3737/1.987)\ \{3.3540 - 2.9142\}10^{-3}) = -1.040$$

Similarly, z-values were calculated for butyl-parahydroxybenzoate in normal butanol, pentanol, hexanol and octanol. A similar calculation was carried out using the non-ideal ϕ_1-value quoted above.

The z-values were regressed on corresponding δ_1-values to find a, b and c of Eqn. 2 for butyl-parahydroxybenzoate. Values obtained by both ideal and non-ideal ϕ_1-values are listed in Table 1. The values of a, b and c for methyl-, ethyl- and propyl-parahydroxybenzoate and for benzoic acid are also listed in Table 1. The consistency of the data can be checked in the sense that the values of a, b and c, as shown in Eqns. 4, 5 and 6 constitute 3 equations giving the values of two unknowns, so that the 3 – 2 = 1 remaining degree of freedom can serve to check internal consistency. For instance (Table 1), for methyl-parahydroxybenzoate:

$$\delta_2 = -2a/b = -2(-36.7)/6.58 = 11.2 \tag{4/5}$$

It is noted that this is in good agreement with values estimated from the graphs of X_2 vs δ_1 reported by Restaino and Martin (1964). V_2 can now be found as:

$$V_2 = bRT/(2\delta_2) = 6.58 \cdot 1.99 \cdot 298/(2 \cdot 11.2) = 174 \tag{5}$$

where the unit of R is the same as that used for ΔH. V_2 can also be found from Eqn. 6:

$$V_2 = -cRT = -(-0.295) \cdot 1.99 \cdot 298 = 175 \text{ ml} \tag{6}$$

in obvious good agreement with the other value. Values calculated in the two fashions for

TABLE 4

EFFECT OF CHANGING ΔH IN EQN. 4, ON THE VALUES OF A, B, AND C IN EQN. 3 AND V OBTAINED FROM EQN. 5/6. BUTYL-PARAHYDROXYBENZOATE

ΔH (cal/mol)	a	b	c	V (Eqn. 5)	δ_2 (Average)
100	−4.11	1.73	−0.15	96.8	5.3
500	−4.78	1.77	−0.15	91.6	5.6
1000	−4.78	1.66	−0.14	84.9	5.8
1868	−6.71	1.81	−0.13	74.6	7.2
3737	−9.63	1.94	−0.10	58.0	9.9
6000	−15.96	2.60	−0.09	57.1	14
7474	−17.36	2.53	−0.07	46.9	16
10,000	−21.8	2.80	−0.04	53.1	25

the parahydroxybenzoic acid esters are listed in the last two lines of Table 1, and it is seen that there is good correlation between the values in all cases.

The surprising feature, however, is that the V_2-values obtained from the regression of z on δ_1 are *not* at all consistent with literature values (line 2 in Table 1). There could be several reasons for this. It is noted first of all that using experimental ϕ-values makes the deviations even more pronounced than when ideal values are used. Another possible explanation could be that ΔH (which is assumed of the same value at T as at T_m) could be in error. For this reason, various trial values of ΔH from extremely low to extremely high were employed. The data calculated in this fashion are shown in Table 4, and it is seen that at (unrealistically) low ΔH-values the V-values start increasing. However, the values of ΔH are now so low that they do not present a feasible solution to the problem. Corrective terms, such as used in Eqn. 9 would give results that parallel those in Table 4.

The present study, hence, has: (a) provided a convenient means of obtaining solubility parameters of solute (δ_2) from solubility vs δ_1 data; (b) has called attention to anomalous values of molar volumes obtained from such solubility plots; (c) has enumerated *some* factors which are *not* the reason for these anomalous values; but (d) does not present an explanation for the anomaly.

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